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(54) Title: COMPOUNDS AND METHODS FOR DIAGNOSING AND TREATING AMYLOID-RELATED CONDITIONS

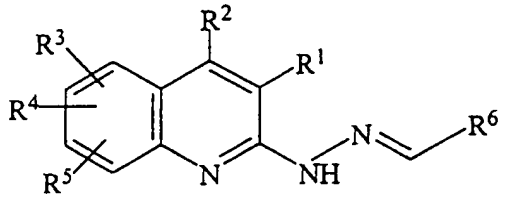
(57) Abstract: The invention provides methods for diagnosing and treating amyloid-related conditions and compounds useful for the same. The invention provides for detecting, imaging, monitoring, diagnosing, and treating conditions characterized by the binding or aggregation of amyloid fibrils. More particularly, the invention relates to using quinolinehydrazone compounds for diagnosing and treating amyloidotic conditions and also as an antioxidant.

AMENDED CLAIMS

[received by the International Bureau on 5 April 2002 (05.04.02);
original claims 30-34 cancelled; remaining claims unchanged (16 pages)]

1. A method for chemically tagging or inhibiting the aggregation of amyloid fibrils comprising the steps of:

(a) providing a compound of the formula:



(I)

or a pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, wherein:

R^1, R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl; and

R^6 is a benzopyridinyl group optionally substituted with one to three substituents selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl;

wherein said alkyl groups at each occurrence are optionally substituted with alkoxy, aryl, or halo; said aryl groups at each occurrence are optionally substituted with alkyl, alkoxy, or halo; and one or more atoms in the compound of formula (I) optionally is replaced with a radiolabeled atom; and

(b) allowing the compound to associate with the amyloid fibrils.

2. The method of claim 1 wherein the radiolabeled atom is selected from the group consisting of ^{3}H, ^{131}I, ^{125}I, ^{123}I, ^{76}Br, ^{18}F, ^{19}F, ^{15}O, and ^{11}C.

3. The method of claim 1 wherein R^1, R^2, R^3, R^4, and R^5 are each independently selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, n-pentyl, t-pentyl, n-hexyl, methoxy, ethoxy, isopropoxy, sec-butoxy, t-butoxy, phenyl, benzyl, trifluoromethyl, trifluoromethylether, and halo.

4. The method of claim 1 wherein the benzopyridinyl group for R^6 is quinolyl or isoquinolyl.

5. The method of claim 1 wherein the compound of formula (I) in step (a) is incorporated in a pharmaceutically acceptable carrier.

6. The method of claim 1 wherein the compound of formula (I) in step (a) is selected from the group consisting of:

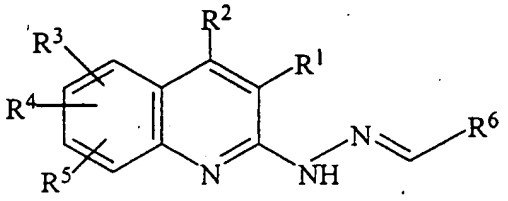
4-methyl-7-methoxy-2-(4-quinolylmethylenehydrazino)quinoline;
4-ethyl-7-methoxy-2-(4-quinolylmethylenehydrazino)quinoline;

4-ethyl-7-ethoxy-2-(4-quinolylmethylenehydrazino)quinoline;
4-methyl-7-ethoxy-2-(4-quinolylmethylenehydrazino)quinoline;
4-ethyl-7-ethoxy-2-(3-quinolylmethylenehydrazino)quinoline;
4-ethyl-7-methoxy-2-(3-quinolylmethylenehydrazino)quinoline;
and
4-methyl-7-methoxy-2-(3-quinolylmethylenehydrazino)quinoline.

7. The method of claim 1 wherein the compound of formula (I) is 4-methyl-7-methoxy-2-(4-quinolylmethylene-hydrazino)quinoline.

8. A method for detecting an aggregation of amyloid fibrils comprising the steps of:

(a) providing a compound of the formula:



(I)

or a pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, wherein:

R^1, R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl; and

R^6 is a benzopyridinyl group optionally substituted with

one to three substituents selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula -OR^7, wherein R^7 is alkyl or aryl;

wherein said alkyl groups at each occurrence are optionally substituted with alkoxy, aryl, or halo; said aryl groups at each occurrence are optionally substituted with alkyl, alkoxy, or halo; and at least one atom in the compound is replaced with a radiolabeled atom;

(b) allowing the compound to associate with the amyloid fibrils to provide a labeled deposit; and

(c) detecting the amount and location of the labeled deposit.

9. The method of claim 8 comprising the steps of detecting the labeled deposit by gamma imaging, magnetic resonance imaging, or magnetic resonance spectroscopy.

10. The method of claim 8 further comprising the step of (d) evaluating or assessing the data obtained in step (c) in an individual and optionally comparing the data with analogous data obtained from a normal human or mammal to identify, assess, or diagnose the medical condition of the individual.

11. The method of claim 10 comprising assessing the condition of an individual undergoing treatment for a condition characterized by the aggregation of amyloid fibrils.

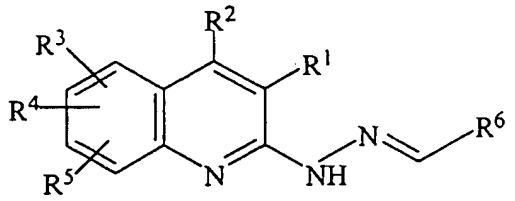
12. The method of claim 11 wherein the condition is selected from the group consisting of Alzheimer's disease, Down syndrome, Type 2 diabetes mellitus, hereditary

cerebral hemorrhage amyloidosis, amyloid A, secondary amyloidosis, familial mediterranean fever, familial amyloid nephropathy with urticaria and deafness, amyloid lambda L-chain or amyloid kappa L-chain, A beta 2M, ATTR, familial amyloid cardiomyopathy, isolated cardiac amyloid, AIAPP or amylin insulinoa, atrial naturetic factor, procalcitonin, gelsolin, crytatin C, AApo-A-I, AApo-A-II, fibrinogen-associated amyloid; and Asor or Pr P-27 or in cases of persons who are homozygous for the apolipoprotein E4 allele, and the condition associated with homozygosity for the apolipoprotein E4 allele; and the treatment comprises administering an active agent selected from the group consisting of doxorubicin, galantamine, tacrine (COGNEX®), selegiline, physostigmine, revistigmin, donepizil (ARICEPT®), metrifonate, milameline, xanomeline, saeluzole, acetyl-L-carnitine, idebenone, ENA-713, memric, quetiapine, neurestrol and neuromidal.

13. The method of claim 8 wherein the compound of formula (I) is a biomarker for the aggregation of amyloid fibrils in an individual.

14. A method for treating a condition in an individual characterized by aggregation of amyloid fibrils comprising the steps of:

(a) providing a compound of the formula:



(I)

or a pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, wherein:

R^1, R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl; and

R^6 is a benzopyridinyl group optionally substituted with one to three substituents selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl;

wherein said alkyl groups at each occurrence are optionally substituted with alkoxy, aryl, or halo; and said aryl groups at each occurrence are optionally substituted with alkyl, alkoxy, or halo;

(b) allowing the compound to associate with the amyloid fibril; and

(c) optionally repeating steps (a) and (b), as necessary, to improve or rehabilitate the condition of the individual.

15. The method of claim 14 wherein the compound of formula (I) is incorporated in a pharmaceutically acceptable carrier.

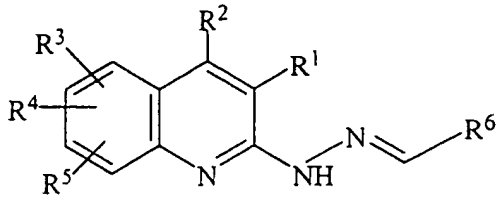
16. The method of claim 14 wherein the condition is selected from the group consisting of Alzheimer's disease, Down syndrome, Type 2 diabetes mellitus, hereditary cerebral hemorrhage amyloidosis, amyloid A, secondary

amyloidosis, familial mediterranean fever, familial amyloid nephropathy with urticaria and deafness, amyloid lambda L-chain or amyloid kappa L-chain, A beta 2M, ATTR, familial amyloid cardiomyopathy, isolated cardiac amyloid, AIAPP or amylin insulinoa, atrial naturetic factor, procalcitonin, gelsolin, crytatin C, AApo-A-I, AApo-A-II, fibrinogen-associated amyloid; and Asor or Pr P-27 or in cases of persons who are homozygous for the apolipoprotein E4 allele, and the condition associated with homozygosity for the apolipoprotein E4 allele.

17. The method of claim 14 wherein the condition is selected from the group consisting of Dutch hereditary cerebral hemorrhage amyloidosis amyloid A, Muckle-wells syndrome, idiopathic-associated amyloid lambda L-chain, myeloma-associated amyloid lambda L-chain, macroglobulinemia-associated amyloid lambda L-chain, idiopathic-associated amyloid kappa L-chain, myeloma-associated amyloid kappa L-chain, macroglobulinemia-associated amyloid kappa L-chain, Portuguese familial amyloid polyneuropathy, Japanese familial amyloid polyneuropathy, Swedish familial amyloid polyneuropathy, Danish familial amyloid cardiomyopathy, systemic senile amyloidosises, isolated atrial amyloid, medullary carcinoma of the thyroid, Finnish familial amyloidosis, Icelandic hereditary cerebral hemorrhage with amyloidosis, scrapie, Cruetzfeld-Jacob disease, Gertsmann-Straussler-Scheinker syndrome, and bovine spongiform encephalitis.

18. A method for delivering a treatment to an individual for a condition characterized by an aggregation of amyloid fibrils comprising the steps of:

(a) providing a composition comprising a compound of the formula:



(I)

or a pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, wherein:

R^1, R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl; and

R^6 is a benzopyridinyl group optionally substituted with one to three substituents selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl;

wherein said alkyl groups at each occurrence are optionally substituted with alkoxy, aryl, or halo; said aryl groups at each occurrence are optionally substituted with alkyl, alkoxy, or halo; in combination with an active agent;

(b) administering the composition to the individual; and

(c) optionally repeating steps (a) and (b), as necessary, to improve or rehabilitate the condition of the

individual.

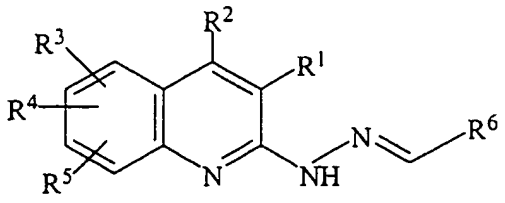
19. The method of claim 18 wherein the active agent is selected from the group consisting of proteins, peptides, carbohydrates, polysaccharides, glycoproteins, nucleic acids, antibodies, peptidomimetics, organic molecules, and fragments or recombinant forms thereof.

20. The method of claim 18 wherein the active agent is selected from the group consisting of inhibitors or activators of a molecule that is required for inhibiting, synthesizing, post-translation modification of, or functioning of, some element involved in the localization or quantification of amyloid; regulators in the spatial or temporal control of expression of a gene product; cytokines, growth factors, hormones, signaling components, kinases, phosphatases, homeobox proteins, transcription factors, translation factors, post-translational factors and enzymes, cholinesterase inhibitors, muscarinic agonists, anti-oxidants, and anti-inflammatory agents.

21. The method of claim 18 wherein the active agent is selected from the group consisting of doxorubicin, galantamine, tacrine (COGNEX®), selegiline, physostigmine, revistigmin, donepizil (ARICEPT®), metrifonate, milameline, xanomeline, saeluzole, acetyl-L-carnitine, idebenone, ENA-713, memric, quetiapine, neurestrol and neuromidal.

22. A method for staining amyloid fibrils comprising the steps of:

(a) providing a compound of the formula:



(I)

or a pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, wherein:

R^1, R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl; and

R^6 is a benzopyridinyl group optionally substituted with one to three substituents selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl;

wherein said alkyl groups at each occurrence are optionally substituted with alkoxy, aryl, or halo; said aryl groups at each occurrence are optionally substituted with alkyl, alkoxy, or halo; and one or more atoms in the compound of formula (I) is replaced with a radiolabeled atom;

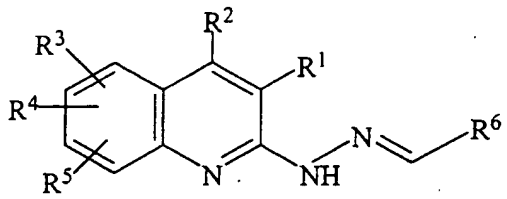
(b) applying the compound to a sample containing amyloid fibrils to form a labeled deposit; and

(c) detecting the labeled deposit.

23. The method of claim 22 wherein the compound is incorporated in a pharmaceutically acceptable carrier.

24. A method for detecting amyloid deposits in biopsy or postmortem human or animal tissue comprising the steps of:

(a) incubating formalin-fixed biopsy or postmortem human or animal tissue with a solution of a compound of the formula:



(I)

or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof, wherein:

R^1, R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl; and

R^6 is a benzopyridinyl group optionally substituted with one to three substituents selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl;

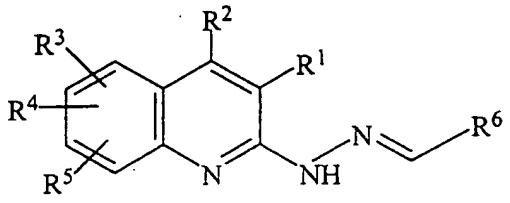
wherein said alkyl groups at each occurrence are optionally substituted with alkoxy, aryl, or halo; said aryl groups at each occurrence are optionally substituted with alkyl, alkoxy, or halo; and one or more atoms in the compound of formula (I) is replaced with a radiolabeled atom; to provide a labeled deposit; and

(b) detecting the labeled deposit.

25. A method for detecting the presence of aggregated prion protein in a mammal, comprising the steps of:

(a) extracting a bodily fluid from the mammal;

(b) contacting the bodily fluid with a compound of the formula:



(I)

or a pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, wherein:

R^1, R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl; and

R^6 is a benzopyridinyl group optionally substituted with

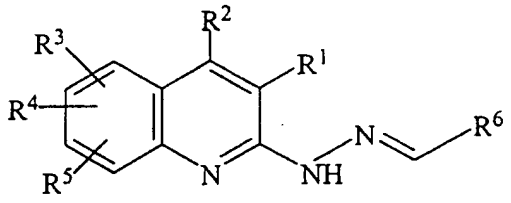
one to three substituents selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula $-OR^7$, wherein R^7 is alkyl or aryl;

wherein said alkyl groups at each occurrence are optionally substituted with alkoxy, aryl, or halo; said aryl groups at each occurrence are optionally substituted with alkyl, alkoxy, or halo; and one or more atoms in the compound of formula (I) is replaced with a radiolabeled atom; to provide a labeled deposit; and

(c) detecting the labeled deposit.

26. A method for providing an antioxidant to an individual, comprising administering a quinolinehydrazone compound to said individual.

27. The method of claim 26, comprising administering a compound of the formula:



(I)

or a pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, wherein:

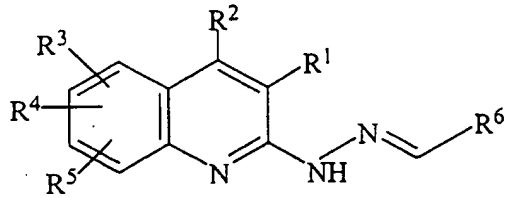
R^1, R^2, R^3, R^4, and R^5 are independently selected from the

group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula -OR^7, wherein R^7 is alkyl or aryl; and

R^6 is a benzopyridinyl group optionally substituted with one to three substituents selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula -OR^7, wherein R^7 is alkyl or aryl;

wherein said alkyl groups at each occurrence are optionally substituted with alkoxy, aryl, or halo; and said aryl groups at each occurrence are optionally substituted with alkyl, alkoxy, or halo.

28. A complex comprising a compound of formula (I), or a pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, in association with or bound to an amyloid fibril, wherein said compound has the formula:



(I)

wherein:

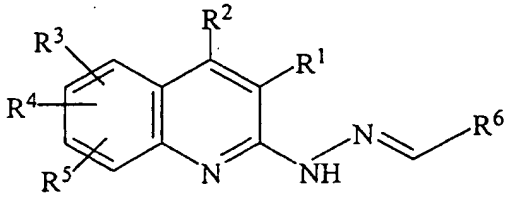
R^1, R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl,

triflouromethyl, trifluoromethylether, halo, and a group of the formula -OR^7, wherein R^7 is alkyl or aryl; and

R^6 is a benzopyridinyl group optionally substituted with one to three substituents selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula -OR^7, wherein R^7 is alkyl or aryl;

wherein said alkyl groups at each occurrence are optionally substituted with alkoxy, aryl, or halo; and said aryl groups at each occurrence are optionally substituted with alkyl, alkoxy, or halo.

29. A complex comprising a compound of formula (I), or a pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, in association with or bound to a prion, wherein said compound has the formula:



(I)

wherein:

R^1, R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group

of the formula -OR^7, wherein R^7 is alkyl or aryl; and

R^6 is a benzopyridinyl group optionally substituted with one to three substituents selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, triflouromethyl, trifluoromethylether, halo, and a group of the formula -OR^7, wherein R^7 is alkyl or aryl;

wherein said alkyl groups at each occurrence are optionally substituted with alkoxy, aryl, or halo; and said aryl groups at each occurrence are optionally substituted with alkyl, alkoxy, or halo.